

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | | | |
|--|--|---|--|--|--|
| (51) International Patent Classification ⁶ : A61K 6/08, C08F 30/04, 30/08 | | A1 | (11) International Publication Number: WO 98/13008 | | |
| (21) International Application Number: PCT/US97/16325 | | (81) Designated States: CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). | | | |
| (22) International Filing Date: 17 September 1997 (17.09.97) | | Published <i>With international search report.</i> | | | |
| (30) Priority Data: 08/721,742 27 September 1996 (27.09.96) US | | | | | |
| (71) Applicant: SOUTHWEST RESEARCH INSTITUTE [US/US]; 6220 Culebra Road, San Antonio, TX 78238-0510 (US). | | | | | |
| (72) Inventor: WELLINGHOFF, Stephen, T.; 7718 Benbrook, San Antonio, TX 78250 (US). | | | | | |
| (74) Agent: SIGALOS, John, L.; Suite 820, 13760 Noel Road, Dallas, TX 75240 (US). | | | | | |
| (54) Title: METAL OXIDE COMPOSITIONS AND METHODS | | | | | |
| (57) Abstract | | | | | |
| Metal oxide and metal oxide-silica nanoparticles are disclosed wherein the surfaces thereof are complexed with a polymerizable, biocompatible, heterocyclic base. Polymerizable compositions are prepared by loading such nanoparticles into acrylate based monomer matrices, which compositions can then be photocured into X-ray opaque, transparent or translucent solids. Methods are disclosed for forming such complexed nanoparticles and compositions and for using such compositions as medical or dental restoratives. | | | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|---------------------------------------|----|---|----|--------------------------|
| AL | Albania | ES | Spain | IS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakhstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

METAL OXIDE COMPOSITIONS AND METHODS

BACKGROUND OF THE INVENTION

The instant invention relates to compositions primarily suitable for dental and medical restoration: i.e., dental fillings or dental and bone adhesive, and to the method of their use 5 for such purposes and methods of manufacture.

There have been repeated efforts to replace amalgam as a filling in dental practice, as well as to have suitable adhesives for dental purposes other than for fillings. One 10 polymeric material that has been suggested for such use is bisglycidylmethacrylate polymer (bis-GMA). When used as a dental adhesive or filling, together with the other usual components admixed therewith, such bis-GMA offers good mechanical and physical 15 properties, but exhibits considerable post-shrinkage and relatively poor adhesion to bone substrate. Thus, it is not entirely satisfactory for use as an adhesive in dental work or as a filling. The use of such GMA material is disclosed in U.S. Patents No. 4,588,756 and 4,964,911.

15 Zero polymerization shrinkage is one of the most necessary features of a dental restorative so that accumulated stresses do not debond the dentin-restorative interface which can result in leakage and microbial attack.

U.S. Patent No. 4,659,751 discusses the use of a variety of acids and other materials in order to treat the surface of teeth, such as enamel and dentin, to activate the surfaces for 20 improved adhesion to polymers, but no disclosure or suggestion is made therein of the use of the GMA or bis-GMA.

In this regard, it is well known that in order to achieve desired bonding on enamel or dentin, the protein coatings on the enamel and the smear layer on dentin must be removed. Traditionally, this has been done utilizing organic acids such as phosphoric, citric, and 25 lactic acids, as well as ethylene diamine dicarboxylic acid. Accordingly, many of the new products provide such polyacids as surface cleaning and priming agents for enamel and dentin. At the present time bis-GMA resins themselves are not inherently adhesive to tooth surfaces, and if used acid etching is required.

30 Nematic liquid crystals are known which can be photopolymerized at high temperature, i.e., 90°C, within seconds with very low polymerization shrinkage to densely

crosslinked networks of reaction extent greater than 95% by the usual free radical methods. The low polymerization shrinkage for such compounds originates from the high packing efficiency that already exists in the nematic state, thus minimizing the entropy reduction that occurs during polymerization.

5 However, polymerization at lower temperatures, such as room temperature, results in undesirable intervening smetic and crystalline phases making them unsuitable as photopolymerized medical and dental restoratives.

SUMMARY OF THE INVENTION

The foregoing problems and deficiencies of the prior art are overcome by the instant
10 invention which provides especially low (essentially zero) polymerization shrinkage in the matrix resin while permitting high loading of strengthening materials and high matrix molecular weight, and yet permitting the matrix to strain soften, and flow onto and/or into areas to be cemented or restored, such as bone and tooth crevices, and be polymerized at room temperature.

15 Briefly, the present invention comprises novel transparent or translucent acrylate (or methacrylate) based matrix-metal oxide compositions. metal oxide nanoparticles with surface complexes, mixed particles formed by such nanoparticles with larger monosized silica particles to improve mechanical strength, and photopolymerizable room temperature nematics that have high strength and hardness with essentially zero shrinkage.

20 The invention also comprises the methods hereinafter set forth for making such tantalum oxide-silica microparticles, for making composites having reduced particle surface acidity, and the method of dental and bone restoration using the noted composites.

DETAILED DESCRIPTION

While the instant invention will be described with particular reference to use in the
25 medical and dental fields, as in bone cements and dental restoratives, because of the high strength, hardness, substantially zero shrinkage, excellent adhesiveness and transparency or translucency of the composites, they can be used in other applications such as adhesives for woods, metals, and the like, or for forming resistant optical coatings and plaques.

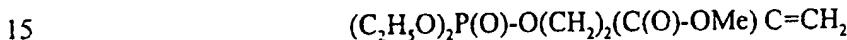
While the present invention is carried out using any metal capable of forming
30 amphoteric metal oxides to form the metal oxide nanoparticles, such as tantalum, niobium,

indium, tin, and the like it will be described in connection with tantalum. Tantalum is particularly desired for dental and medical uses since it will provide X-ray opaque materials necessary for subsequent review of the treated site; i.e., tooth or bone, by dentists and doctors.

5 These tantalum nanoparticles are prepared as set forth in U.S. Patent No. 5,372,796 by ester exchange of tantalum oxide with an acid such as formic acid.

For this invention it is important that such nanoparticles be non-interacting without high surface acidity. High surface acidity is detrimental for dental applications.

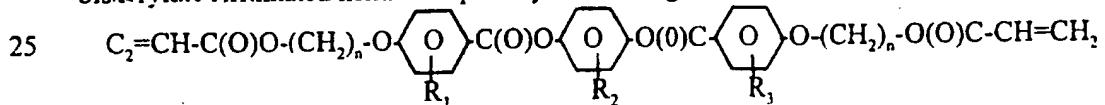
10 Accordingly, a polymerizable, biocompatible, heterocyclic base that can complex the acid sites on the surface of the tantalum oxide nanoparticles is admixed therewith. It is preferred to use alkene terminated imidazoles and phosphates for this purpose with specific examples being 1-vinyl imidazole (VIM) and the phosphonated acrylic ester, PHEMA, formed by reacting diethylchlorophosphate with hydroxyethyl methacrylate (HEMA) in the presence of triethylamine in ether. Such PHEMA has the formula:



It will be evident that other like polymerizable imidazoles and phosphates can be utilized with, for example, compounds in which a liquid crystal moiety of the type set forth below is inserted between the alkene and imidazole or alkene and phosphate moieties.

20 Such complexed tantalum oxide nanoparticles with imidazole or phosphate termination have no particle interaction or network formation and have enhanced coupling with the matrix resin(s).

As to the matrix monomers there are used photopolymerizable, acrylate based monomers, particularly those useful in dental applications. Particularly preferred are the bisacrylate terminated nematic liquid crystals having the formula:



In this formula n is a C_6 to C_{12} substituted or unsubstituted alkyl group, R_1 and R_3 are H or a methyl group and R_2 is a bulky group (a group of providing steric hindrance), such as a tertiary butyl group and the like. This large group size "mismatch" between the central aromatic group and the two surrounding aromatic groups is required to achieve in the final

product a nematic state at room temperature while suppressing crystallinity at the same temperature.

The methacrylic derivates of the above diacrylates are also suitable. Also, as discussed below, bis-GMA and other bis-GMA and other bis-glycidylacrylate and 5 methacrylate compounds can be included in the matrix.

The method of making metal oxide clusters set forth in U.S. Patent 5,372,796 permits growth of tantalum oxide particles of 1-2 nm in diameter. Assuming perfect bonding between the particle and matrix, a decrease in particle size at a given volume fraction of particles will increase the elastic constraint on the deforming matrix molecules and lead to 10 an increase in modulus. However, as the particle size approaches molecular dimensions, the very closely spaced crosslinking points of high functionality within the matrix will substantially quench any large scale molecular motions. It is these motions which are important for energy dissipation and fracture toughness.

Thus, for the purposes of this invention, particles sizes in the 50-100 nm sizes are 15 more suitable. Also, the X-ray opacity of a composite material made from only tantalum oxide particles is too high for optimum diagnostic sensitivity. Therefore, in accord with the instant invention the Ta-nanoparticles are combined with relatively large, preformed silica particles has the advantage of increasing particle size and reducing X-ray opacity.

Monosized silica particles in the 10-20 nm diameter range are commercially available, 20 but some are only stable as individual non-interacting particles at basic pH, where coagulation of the tantalum oxide nanoparticles will occur. Silica particles of 12 nm that are stable at acidic pH are available with a 13% aluminum oxide coating. These are supplied as concentrated water solutions that are stable at pH=4.5 and, in addition, are positively charged with chloride counterions. It has been found that when the naturally 25 acidic methanol solutions of tantalum oxide nanoparticles are mixed with water solutions of this silica particle positive sol, clear stable solutions result which indicate excellent compatibility.

When the solvent is removed from this mixture, gelation occurs with subsequent 30 insolubilization of the oxides. However, for Ta-oxide silica ratios >2, the addition of a strong complexing agent such as triethylphosphate or other organic phosphates permits

complete solvent evaporation and subsequent dissolution into methanol. Substantial reduction of particle acidity is also observed when the surface protons on the tantalum oxide particles combine with chloride counterions of these silica particles and escape as HCl during vacuum evaporation. For weight ratios of Ta-oxide/silica between 2 and 1, 5 heterocoagulation takes place and then even the phosphate-complexed oxide is insoluble.

Organic phosphate triesters are known to be strong complexing agents for many metal ions with the potential to extract metal ions into hydrophobic phases. in order to take advantage of this complexing potential, the Ta₂O₅-SiO₂ composite is reacted with PHEMA. While PHEMA is a liquid at room temperature and is insoluble in water, it can be made 10 soluble in water by the addition of a small quantity of methanol.

With this type of compound, the strategy is to utilize the diethylphosphate terminus to bind to the nanoparticle surface and use the methacrylate end to copolymerize and couple the nanoparticles into the matrix resin.

In a typical procedure 40 wt.% of a 2:1 Ta₂O₅-SiO₂ composite with 60 wt% PHEMA 15 was prepared by dissolving SiO₂ particles and PHEMA in a methanol solution of Ta-oxide nanoparticles, and pumping the mixture dry at room temperature. The resultant gel was redissolved in methanol to form a clear mixture-indicating that the resulting nanoparticles were independent and non-associated, as intended. It was also found that bis-GMA can be partially substituted for PHEMA (up to 50 wt%) to make similar clear solutions.

20 The results of these studies establish the feasibility of using both imidazole and phosphate termination to attach reactive species to nanoparticle surfaces so as to prevent particle interaction and network formation, and to enhance coupling to the matrix resin. They also demonstrate alternative routes to producing Ta₂O₅/SiO₂ composite particles with variable x-ray absorbance, in the optimum size range of 50- 100 nm.

25 Dental practice requires that the matrix materials be fluids between room temperature and body temperature. Liquid crystalline diacrylates such as, bis-(4-(10-acryloyloxyalkyl-1-oxy)benzoyl)2-(t-butyl) quinones and methacrylo derivatives are especially useful for this purpose. Although molecules of this structure have been synthesized, practical application in low polymerization shrinkage applications was 30 precluded because of the development of crystallinity at room temperature which

effectively prevents manipulation of the material. However, the novel substitution of the central aromatic group with an especially bulky group such as t-butyl was found to suppress crystallinity at room temperature while still permitting the nematic state to exist.

Thus, tests with bis-(4-(10-acryloyloxydecyl-l-oxy)benzoyl)2-t-butyl quinone, 5 [C10(H,TB,H)] and bis-(4-10-acryloyloxyhexyl-l-oxy)benzoyl)2-t-butyl quinone, [C6(H,TB,H)], were nematic in this temperature range and could be photopolymerized to strong solids with 1-2% polymerization shrinkage. However, substitutions, such as (C10(H,H,H), C10(H,Me,H), C10(H,MeO,H), C6(11,Me,H), C11(MeO,TB,MeO), C11(MeO,H,Me) and C11(MeO,Me,MeO) all resulted in materials with melting points of 10 50°C. As previously noted, achieving a nematic state at room temperature while suppressing crystallinity at the same temperature requires a large side group size mismatch between the central aromatic group and the two surrounding aromatic groups.

Even though liquid crystalline materials such as C10(H,H,H) melted above room temperature (ca85°C) dilution of C10(H,H,H) with 50wt%bisGMA generated a mobile 15 liquid crystalline phase at room temperature (28°C). This mobile liquid crystal phase converted to an isotropic phase at 63°C.

It was possible to mix HEMA coated tantalum oxide nanoparticles prepared as above with this phase by co-dissolution of a HEMA solution of the nanoparticles in methanol with a methanol solution of the C10(H,H,H) and bis-GMA and subsequent evaporation of 20 the methanol. The mobile room temperature liquid crystal phase of 52wt%Ta,34%C10(H,H,H), 14% HEMA converted to an isotropic phase at 70°C.

While bis-GMA can be included as part of the matrix, other C₁ to C₁₂ acrylates and methacrylates can be used, such as bis-glycidylmethacrylate, bis-glycidylethylacrylate, bis-glycidylethylmethacrylate, 2-hydroxyethylmethacrylate, mixtures thereof, and the like.

25 The amount of nanoparticles added to the matrix can vary widely. Amounts of up to 40 wt. % of nanoparticles for 100 wt. % of nanoparticles and matrix, can be utilized. At amounts above about 40 wt. % the admixture becomes pasty. Obviously, the amount of loading is in the range necessary to give the desired final product and thus can be determined for such particular nanoparticle and matrix used by routine experimentation.

In using the transparent or translucent nanoparticle-matrix composition, it need only be applied to the surface to be treated and photopolymerized. Thus, for use as a dental restorative, the liquid or pasty composition is placed on the tooth by a dentist or dental technician and ultra-violet light used to effect the polymerization (cure) into a high

5 strength, hard, transparent, X-ray opaque coating, or filling, with essentially zero shrinkage. Such essentially zero shrinkage is most important for fillings. Also, the transparency or translucency is an important characteristic, because it permits deeper photocure in thicker layers of the restorative composition, thus avoiding the multiple applications of opaque photocured restoratives presently used.

10 While the invention has been described in connection with a preferred embodiment, it is not intended to limit the scope of the invention to the particular form set forth, but on the contrary, it is intended to cover such alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

Claims

What is claimed is:

1. Metal oxide nanoparticles having surfaces complexed with a polymerizable, biocompatible heterocyclic base.
- 5 2. The nanoparticles of Claim 1 wherein the metal is tantalum and the base is an alkene terminated imidazole or phosphate.
3. The nanoparticles of Claim 2 wherein the base is 1-vinyl imidazole or $(C_2H_3O)_2P(O)-O(CH_2)_2(C(O)-OMe)C=CH_2$.
4. Metal oxide-silica nanoparticles composites with surfaces complexed with a 10 polymerizable, biocompatible heterocyclic base.
5. The nanoparticles of Claim 4 wherein the metal is tantalum and the base is an alkene terminated imidazole or phosphate.
6. The nanoparticles of Claim 5 wherein the base is 1-vinyl imidazole or $(C_2H_3O)_2P(O)-O(CH_2)_2(C(O)-OMe)C=CH_2$.
- 15 7. A composition photopolymerizable into transparent or translucent solids comprising an acrylate based monomer matrix containing metal oxide nanoparticles or metal oxide-silica nanoparticles having surfaces complexed with a polymerizable, biocompatible heterocyclic base.
8. The composition of Claim 7 wherein the metal is tantalum and the base is an 20 alkene terminated imidazole or phosphate.
9. The composition of Claim 8 wherein the base is 1-vinyl imidazole or $(C_2H_3O)_2P(O)-O(CH_2)_2(C(O)-OMe)C=CH_2$.
10. The method of making metal oxide nanoparticles with complexed surfaces 25 comprising reacting the nanoparticles with a polymerizable, biocompatible heterocyclic base at a temperature and for a time sufficient to complex said surfaces.
11. The method of Claim 10 wherein said nanoparticles are tantalum oxide nanoparticles or tantalum oxide-silica composite nanoparticles and said base is an alkene terminated imidazole or phosphate.

12. The method of Claim 11 wherein the base is 1-vinyl imidazole or $(C_2H_5O)_2P(O)-O(CH_2)_2(C(O)-OMe)C=CH_2$,
13. The method of making photopolymerizable, transparent or translucent X-ray opaque compositions comprising admixing a metal oxide nanoparticles having surfaces complexed with a polymerizable, biocompatible heterocyclic base and an acrylate based monomer.
5
14. The method of Claim 13 wherein said nanoparticles are tantalum oxide nanoparticles or tantalum oxide-silica composite nanoparticles with said base in an alkene terminated imidazole or phosphate.
- 10 15. The method of Claim 14 wherein the base is 1-vinyl imidazole or $(C_2H_5O)_2P(O)-O(CH_2)_2(C(O)-OMe)C=CH_2$,
16. The method of dental repair comprising applying to a dentin surface the photopolymerizable composition of Claim 7 and then photopolymerizing said composition.
- 15 17. The method of Claim 16 wherein the metal is tantalum and the base is an alkene terminated imidazole or phosphate.
18. The method of Claim 17 wherein the base is 1-vinyl imidazole or $(C_2H_5O)_2P(O)-O(CH_2)_2(C(O)-OMe)C=CH_2$,

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/16325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 6/08; C08F 30/04, 30/08
US CL :523/120, 212, 213; 524/547; 526/240, 241

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 523/120, 212, 213; 524/547; 526/240, 241

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 5,337,129 A (BADESZA) 09 August 1994. | 1-18 |
| A | US 5,316,855 A (WANG et al) 31 May 1994. | 1-18 |
| A | US 5,231,156 A (LIN) 27 July 1993. | 1-18 |
| A | US 5,064,877 A (NASS et al) 12 November 1991. | 1-18 |

 Further documents are listed in the continuation of Box C. See patent family annex.

| | | |
|---|-----|--|
| • Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| • "A" document defining the general state of the art which is not considered to be of particular relevance | | |
| • "E" earlier document published on or after the international filing date | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| • "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| • "O" document referring to an oral disclosure, use, exhibition or other means | | |
| • "P" document published prior to the international filing date but later than the priority date claimed | "Z" | document member of the same patent family |

Date of the actual completion of the international search

30 OCTOBER 1997

Date of mailing of the international search report

04 DEC 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

BERNARD LIPMAN

Telephone No. (703) 308-2351